by the Examiner, and, by so doing, to advance the prosecution of the application to allowance.

By this amendment, Applicants have cancelled claims 1-24, without prejudice or disclaimer and have added new claims 25-44. All of the added claims are fully supported in the as-filed specification.

New claims 25-33 and 35-38 have been drafted as "process claims". New claim 33 has been redrafted to introduce a proper antecedent basis for the objected to term "the cells" in claim 33.

Claims 25 to 34 and 40-44 better define the scope of the invention in view of the Valentini et al. reference.

These newly drafted claims are fully supported in the originally filed specification generally, and in particular at page 5, lines 23-30.

Accordingly, it is respectfully submitted that the §112, second paragraph, rejection has been overcome, and its withdrawal is respectfully solicited.

The newly drafted claims also serve to overcome the rejection under 35 U.S.C. §101, and this rejection should also be withdrawn.

Claims 1-24 stand rejected under §103(a) as being unpatentable over Burns et al., alone or in view of Cialdi et al., or Khan et al., or Nicholas et al. This rejection is respectfully traversed.

According to the Examiner, claims 1-24 read on "*a matrix comprising hyaluronic acid or a derivative thereof and a biological material comprising said matrix and intestinal cells*".

In particular, according to the Examiner, Burns et al., disclose "a matrix comprising derivatives of HA and cells, used as support for cell proliferation and placed at the site of

skin lesions, including ulcers", and it would therefore have been obvious to one of ordinary skill in the art at the time the invention was made, to use the teachings of Burns et al., for preparing the present matrix and biological material, also in view of Cialdi et al., Khan et al., and Nicholas et al., which provide HA derivatives.

The Examiner has also rejected the claims under §103 (a) over Valentini et al. According to the Examiner, Valentini teaches porous scaffolds made of HA derivatives which are able to be used for the treatment of ulcers and to promote tissue culture, and it therefore renders the present invention *prima facie* obvious to a person of ordinary skill in the art.

Before commenting on the specific rejections raised by the Examiner, applicants wish to point out that the gist of the claimed invention is to provide a biological material containing suitable cell cultures for generating the walls or filling diverticula in the digestive apparatus or system.

As pointed out at page 3, lines 8-11, where a loss or a degeneration of a large area of tissue or a perforation of the digestive apparatus walls has occurred, there is a long-felt need for a biological material which when implanted onto the lesion site is able to reconstruct the injured part.

The Applicants have solved this technical problem by grafting cells – in particular intestinal cells – on scaffolds made of hyaluronic acid derivatives, thus obtaining the biological material, as claimed in claims 34 and 39-44, that can be implanted onto the lesion site by surgery.

These results could in no way have been predicted or suggested from the teachings of the cited references.

Burns et al., discloses compositions containing a water-insoluble polyanionic polysaccharide derivative, including hyaluronic acid (hereinafter referred to as HA).

Concerning this, the Examiner observed that, even if Burns et al., does not specify all the HA derivatives contemplated in the instant application, nevertheless he teaches that derivatives of polysaccharide include the addition of functional groups, such as substituted amide groups, ester linkages and amine groups, and reactions that increase the water insolubility by crosslinking the polysaccharide molecules or non-covalent interactions.

Furthermore, as correctly noted by the Examiner, the compositions according to Burns et al., can also be provided *"as a composite matrix to support cell and tissue growth and proliferation"* (see Burns et al., col. 3, line 8 and ff).

An important point has, however, been omitted by the Examiner. The composition disclosed by Burns et al., contains **as an essential component** a hydrophobic bioabsorbable polymer, chosen, for example, from amongst polylactones, polydioxanones, polyglicolide, etc., which is combined with the polysaccharide, for example, by coating the polysaccharide with the hydrophobic polymer.

Besides the hydrophobic polymer, which is always present in the compositions according to Burns et al., the HA is preferably mixed with another polyanionic polysaccharide and activated by reacting with a carbodiimide. In fact, all of the compositions disclosed by Burns et al. in their Examples always contain HA and carboxymethylcellulose (CMC) modified with a carbodiimide, and is then combined with a hydrophobic polymer.

In point of fact, **the claimed matrix only comprises HA or derivatives thereof**, which are not modified with carbodiimide, nor combined with an hydrophobic polymer.

According to the claimed invention, **no other compon nt in addition to HA or a d rivative th reof is necessary** to obtain a matrix useful as support for cellular growth for preparing the present biological material.

Therefore, from the disclosure of the Burns et al., composition, it could not be **foreseen** that the present matrix comprising only HA or derivatives thereof would be capable of growing intestinal cells and producing a biological material able to treat ulcers, lesions and diverticula of the digestive and gastrointestinal apparatus.

Applicants wish to point out that the experiments described by Burns et al., at the end of each Example, highlight the improved properties of the compositions containing polysaccharide plus hydrophobic polymer, when compared to the polysaccharide alone.

Such properties concern the reduction in post-surgical adhesion formation or higher tensile strength, but make no reference whatever to the ability of the compositions to grow intestinal cells and to produce a biological material to be used for reconstructing lesion sites in the gastrointestinal tract. In fact, this application was not even investigated by Burns et al.

Therefore, from the Burns et al. teachings, a person of ordinary skill in the art would in no way have a reasonable expectation that the present matrix which is only made of unmodified HA or derivatives thereof, without a hydrophobic polymer, would be successful for the claimed use.

As to the secondary references cited by the Examiner, Cialdi et al., Khan et al., and Nicholas et al., they disclose some of the HA derivatives as being of possible use in the present biological material, but, they add nothing to the Burns et al. teachings.

It is respectfully submitted that claims 25-44 distinguish over the combination of references employed by the Examiner. Accordingly, withdrawal of the §103(a) rejection is, accordingly, solicited.

As noted by the Examiner, Valentini et al., discloses scaffolds made of HA derivatives constituted by a **three-dimensional structure of interconnected pores** upon which cells may be grown.

The scaffolds described by Valentini et al., are characterized by a porous structure, having a void volume ranging from 40% to 90%.

In order to obtain such a material, Valentini et al., must use HA derivatives that are water-insoluble, but which are water-soluble in a first solvent, wherein the HA derivative is dissolved together with a pore forming agent that is insoluble in this first solvent. Then this mixture is contacted with a second solvent in which the HA derivative is insoluble, but in which the pore forming agent is soluble. In this manner, a porous scaffold of water-insoluble HA derivatives comes out of solution, wherein the pore forming agent remains dissolved. (See Valentini et al., Col. 4, line 45-62).

This process allows the preparation of a sort of sponge having interconnected pores of sufficient size to permit the growth of cells into the pores. The desirable porosity for cell ingrowth, as well as the interconnectivity of the pores are essential aspects of the Valentini et al. invention. In fact, only those techniques that do not adversely affect the structural integrity of these scaffolds are permitted to be used according to Valentini et al., whereas freeze-drying techniques and elevated temperatures must be avoided (see Valentini et al., col. 7, lines 22-35).

Therefore, the scaffolds according to Valentini et al., even when they contain the same HA derivative as the present invention, are nonetheless completely and utterly different in their structure. In fact, the claimed HA derivatives matrix which can only be in the form of a **perforated membrane** or in the form of **non-woven tissue** is completely and utterly different physical forms from the Valentini et al. **sponges.**

As a matter of fact, a non-woven fabric made of HA or HA derivatives can be described as a web composed of a large quantity of fibres, joined together by chemical coagulation or mechanical means, or with the aid of cohesive material, thus producing a structure composed of haphazardly placed, matted fibres, constituting a soft, resistant material. A perforated membrane made of HA or HA derivatives is a membrane comprising a series of holes of a defined and constant size separated from each other by a constant distance, obtainable using mechanical perforation devices or thermal and UV lasers on a continuous membrane.

The distinction between the applicants' claimed matrix and the spongy scaffold disclosed by Valentini et al. is therefore readily evident.

It should be noted that new claims 25, 34 and 40-44 now recite and highlight the differences between applicants' claimed matrix and the Valentini et al. scaffold.

Moreover, the very particular porous structure of the scaffolds disclosed by Valentini et al., renders them useful in the repair of bone and cartilage defects, by seeding bone cells or bone cell precursors, and chondrocytes or cartilage cell precursors, on the scaffold before implantation.

As correctly noted by the Examiner, Valentini et al. also reports on the fact that the scaffolds may be used for the treatment of ulcers (see Valentini et al., col. 7, line 52 to col. 8, line 17).

With respect to this, applicants wish to highlight that the use in the treatment of ulcers is only cited by Valentini et al. **among a plethora of very different and only potential uses,** that are in fact neither developed, nor exemplified, nor enabled.

By contrast, the present biological material is used **specifically for regenerating the walls or filling diverticula** in **the digestive apparatus.**

In particular, as is clearly pointed out at page 3, line 8-11, the presently claimed biological material has the ability and the scope to solve the technical problems consisting in the reconstruction of injured parts of the digestive apparatus, where there **is a loss or degeneration of a large area of tissue or perforation of the wall,** whereas Valentini et al., only discloses the implantation of scaffolds of a few millimeters in size to repair defects in bones (see Valentini et al., col. 11, Example 3, line 31-57).

In conclusion, the present invention can in no way be considered as being obvious in view of the scaffolds according to Valentini et al. for the following reasons:

i) Valentini et al., discloses HA derivatives scaffolds in the form of sponges with interconnected pores, whereas the presently claimed biological material comprises a matrix in the form of perforated membranes or non-woven tissue;

ii) Although Valentini et al. encompasses the administration of the scaffolds by means of surgical implantation, the scaffold is implanted on small sites. Therefore, this reference could in no way suggest to the person of ordinary skill in

gastrointestinal repair that the present biological material, when implanted onto the lesion site, is able to repair and regenerate large areas of degenerated or injured tissue.

Since claims 25-44 distinguish over Valentini et al., the §103(a) rejection has been overcome since a *prima facie* case of obviousness has not been established. It should, accordingly, be withdrawn.

The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees to our Deposit Account No. 01-0035.

Respectfully submitted,

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